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## Title

Paediatric Chronic Fatigue Syndrome: 25 year perspective

## Authors

Loades, M.E.<sup>1,2</sup>, Crawley, E.<sup>2</sup>, Chalder, T.<sup>3,4</sup> & Flannery, H.,<sup>5</sup>

## Affiliations

<sup>1</sup> Department of Psychology, University of Bath

<sup>2</sup> Bristol Medical School, University of Bristol

<sup>3</sup> King's College London

<sup>4</sup> South London & Maudsley NHS Foundation Trust

<sup>5</sup> Child and Adolescent Psychology Team, Paediatric and Adolescent Division, University College London Hospitals NHS Foundation Trust, UK

## Corresponding author contact details

Maria Loades, Department of Psychology, University of Bath, Bath, BA2 7AY, England.

Email [m.e.loades@bath.ac.uk](mailto:m.e.loades@bath.ac.uk) (+44) 01225 385249; BA(Cantab), DClinPsy

## Co-author contact details & qualifications

Professor Esther Crawley, [esther.crawley@bristol.ac.uk](mailto:esther.crawley@bristol.ac.uk), PhD, Centre for Child and Adolescent Health, 1-5 Whiteladies Road, Bristol, BS8 1NU.

Professor Trudie Chalder, [trudie.chalder@kcl.ac.uk](mailto:trudie.chalder@kcl.ac.uk), PhD, King's College London, Department of Psychological Medicine, E3.04, 3rd floor, East Wing, Institute of Psychiatry, Psychology & Neuroscience, King's College London, 16, De Crespigny Park, London, SE5 8AF  
South London and Maudsley NHS Foundation Trust, Monks Orchard Road, Beckenham, Kent, BR3 3BX.

Dr Halina Flannery, [halina.flannery@nhs.net](mailto:halina.flannery@nhs.net), DClinPsy, Child and Adolescent Psychology Team, Paediatric and Adolescent Division, University College London Hospitals NHS Foundation Trust, 6th Floor, London NW1 2PG

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## Conflicts of Interest

EC acts as a non-paid medical advisor for the Sussex and Kent ME society. TC is the author of several self-help books on chronic fatigue for which she has received royalties. TC/KCL has received ad hoc payments for workshops carried out in LTCs. KCL have received payments for TC's editor role in JoMH. TC co-authored a book called "Overcoming Chronic Fatigue in Young People" for which she receives royalties. The other authors declare that there is no conflict of interest.

Over the lifetime of *Clinical Child Psychology and Psychiatry*, there has been considerable progress in understanding the epidemiology of Chronic Fatigue Syndrome (CFS), also known as myalgic encephalomyelitis (ME) and some progress in testing treatment approaches. Twenty-five years ago, clinicians and researchers did not believe that CFS existed in primary school children, little was known about the experience of children, and there were no randomised controlled trials testing treatment approaches. In this review, major developments in epidemiology, knowledge about clinical presentations and correlates, impact of CFS and treatment approaches will be highlighted. We are clinicians and researchers working in specialist CFS services in the United Kingdom.

CFS has been a defined diagnostic entity since 1991 (Sharpe et al., 1991). There are several different diagnostic frameworks for diagnosing CFS (Carruthers et al., 2011; Fukuda et al., 1994; NICE, 2007; Sharpe et al., 1991). All include ongoing, debilitating fatigue which is not secondary to another medical condition or to exertion. Concomitant symptoms include general malaise, headaches, muscle and joint pain, nausea, disrupted sleep, dizziness and cognitive difficulties. Initially, the diagnostic criteria for adults were applied to children and young people. In 2004, the Royal College of Paediatrics and Child Health (RCPCH, 2004) recommended that fatigue lasting > 3 months was sufficient, a shorter duration than is required for adults. This has been reflected in some but not all the diagnostic frameworks. Here, we predominantly draw on evidence from clinical cohorts with a confirmed CFS diagnosis and evidence from general population studies of chronic debilitating fatigue, not necessarily formally assessed and diagnosed CFS.

## Changes in Epidemiology

25 years ago, we did not know how common CFS was in teenagers, and whether it even existed in primary school aged children. The evidence base for the prevalence, incidence, and risk factors in paediatric CFS has since developed considerably.

A recent systematic review and meta-analysis of prevalence studies found 6 studies in children and adolescents, with an estimated prevalence of 0.89% although there was considerable heterogeneity and most studies were in Western countries (Lim et al., 2020). Incidence rates have also varied. The incidence of CFS over 4 to 6 months was found to be 0.5% in the general population of 11 to 15-year olds in England (Rimes et al., 2007), whilst in Holland, the incidence of CFS diagnosed by paediatricians was 12 per 100 000 (Nijhof et al., 2011). The incidence of paediatrician diagnosed CFS varied by geographical region in 10 to 17-year olds in Australia, ranging from 1.31-17.48 per 100 000, and was much lower (0.25 per 100 000) in 4 to 9-year olds (Knight et al., 2019).

In the last 25 years, the epidemiology of CFS has become better understood. Several risk factors have been identified including female gender after puberty (before puberty, this is almost equal)(Collin et al., 2015), and social adversity (Crawley et al., 2012). Some studies have found that anxiety and depression are associated with a higher risk of developing chronic fatigue over the course of 4 to 6 months (Rimes et al., 2007), although in the ALSPAC cohort, depressive symptoms at age 9 and 13 were not associated with chronic disabling fatigue at age 16 once co-morbid depressive symptoms were accounted for (Collin et al., 2019). In the same cohort low levels of physical activity (Collin, Norris, Deere, et al., 2018) and shorter night-time sleep duration and difficulties in going to sleep (Collin, Norris, Gringras, et al., 2018) were found to be associated with subsequent chronic disabling fatigue.

There does not appear to be a single cause or trigger for CFS. For some, the onset of symptoms is gradual, whilst for others, it is sudden (Knight et al., 2019). Many young people report a history of having a physical illness like glandular fever or Epstein-Barr virus (Katz et al., 2009), and a sense that they never really recovered afterwards (Knight et al., 2019). For some, the trigger could have been brought about by a highly stressful or traumatic event as adults with CFS are more likely to have

experienced childhood trauma (Heim et al., 2009), however this is less common and less well understood in children. It appears that a range of biopsychosocial variables are predictive of post-infectious fatigue; predictors of developing chronic fatigue following Epstein-Barr virus in adolescents included heightened pain sensitivity and sensory sensitivity, greater functional impairment, higher anxiety, better verbal memory, elevated plasma C reactive protein and lower plasma vitamin B12, but not viral load or blood lymphocyte count for example (Pedersen et al., 2018; Pedersen, Asprusten, Godang, Leegaard, Osnes, Skovlund, Tjade, Oie, et al., 2019).

## Knowledge about Clinical Presentations and Correlates

Compared to 25 years ago, we now understand more about the symptom presentation, behavioural responses and the cognitive and emotional features of CFS in adolescents particularly, although less is known about primary school aged children.

### *Symptom presentation*

25 years ago, it was presumed that CFS looked the same irrespective of age. We now have a greater understanding of how CFS presents in children and adolescents as compared to adults. There are early indicators from reasonably large observational cohorts in two countries that children present with different symptoms depending on age. Younger children tend to have sore throats but are less likely to have cognitive symptoms (Collin et al., 2015). Adolescents tend to have headaches and co-morbid depressive symptoms but are less likely to have palpitations, general malaise, pain, tender lymph nodes, dizziness, and co-morbid anxiety symptoms (Collin et al., 2015). These differences could reflect underlying differences in aetiopathology.

### *Behavioural responses*

Twenty-five years ago, children and young people with CFS were assumed to be relatively physically inactive. There is now evidence that is true for many but not all (Solomon-Moore et al., 2019).

Children and young people may respond to their symptoms by booming and busting , where they push themselves to do as much as they can which tends to result in an exacerbation in fatigue symptoms, or avoiding activities and resting, The latter pattern is associated with subsequent impairments in physical functioning (Loades, Rimes, Lievesley, et al., 2019a). Doing light activity was associated with better physical functioning and lower fatigue, compared to being inactive (Solomon-Moore et al., 2019).

### *Cognitive responses*

Cognitively, adolescents with CFS are more likely to have negative thoughts about their symptoms that are potentially unhelpful for recovery than adolescents with asthma (Loades, Rimes, Lievesley, et al., 2019a), including endorsing high levels of fear avoidance beliefs (e.g. fearing that activity will make the symptoms worse)(Loades et al., 2020). These thoughts may reflect the reality of their experience but may also get in the way of recovery. Some of these patterns of thinking, particularly damage beliefs (e.g. believing that symptoms themselves show that damage is being caused to the body) and catastrophising (e.g. believing that they will never feel right again), are associated with subsequent fatigue and functioning (Loades, Rimes, Lievesley, et al., 2019a). Parents' beliefs about their adolescent offspring's symptoms are associated with the adolescent's own beliefs (Loades, Rimes, Lievesley, et al., 2019a).

Attributions that children and families make about their illness could impact on recovery. Research found that most adolescents with CFS (and their parents) believe that CFS was caused by a virus and/or contextual factors and stress (Loades et al., 2018). After Epstein-Barr virus specifically, fatigue has been found to be associated with illness perceptions, including beliefs about causality (Pedersen, Asprusten, Godang, Leegaard, Osnes, Skovlund, Tjade, Øie, et al., 2019). Whatever the trigger, we know that adolescents have lower perceived control over their illness and perceive there

to be more severe consequences of it compared to those with type 1 diabetes or juvenile arthritis (Haines et al., 2019).

Certain beliefs about emotions, such as believing that negative emotions are unacceptable, and should be avoided, can cause problems in the development of emotional regulation and emotional processing skills. This can result in suppressing, ignoring, or avoiding emotions. Although theoretical models of CFS developed in the 1990s, for example, Surawy et al. (1995), suggested that beliefs about emotions may contribute to the maintenance of CFS, there is evidence that these beliefs are similar in adolescents with CFS to those of other adolescents and do not appear to be predictive of subsequent fatigue or functioning (Loades, Rimes, Lievesley, et al., 2019b).

### *Emotional responses*

Emotionally, a substantial minority of young people with CFS also meet the criteria for co-morbid mental health problems, particularly depression and anxiety (Bould et al., 2011; Loades et al., 2017) Loades et al, 2020). In adolescents with chronic fatigue after Epstein Barr virus, fatigue severity was found to be associated with concurrent anxiety and with subsequent depression (Pedersen, Asprusten, Godang, Leegaard, Osnes, Skovlund, Tjade, Oie, et al., 2019). In people with established CFS depressive symptoms at one point in time explain some of the variance in subsequent fatigue (Loades, Rimes, Ali, & Chalder, 2019).

## Impact

25 years ago, there were some initial indications of the devastating impact CFS had on functioning (Walford et al., 1993). Although the impact on children and young people's lives has not changed, we now understand far more about it.

At an individual level, children and adolescents describe the extensive disruptive effects of CFS on physical ability, social life and on the self (Parslow et al., 2017). Affected children miss considerable amounts of school (Crawley & Sterne, 2009; Knight et al., 2018) and school attendance is more severely curtailed than in other paediatric conditions including migraine (Smith et al., 2003), inflammatory bowel disease (Richards et al., 2005), juvenile idiopathic arthritis and mood disorders (Gray et al., 2001). Academic performance is also severely compromised, even when controlling for other relevant factors such as IQ (Knight et al., 2018). Having CFS gets in the way of peer relationships (Richards et al., 2005) and interferes with doing leisure activities (van Middendorp et al., 2001), as well as activities of daily living (Garralda & Rangel, 2004). Quality of life overall has been found to be lower in CFS compared to healthy controls (Carroll et al., 2018; Roma et al., 2019).

For families, paediatric CFS is associated with a loss of monthly income and an increase in monthly expenditure, as well as parental distress (Missen et al., 2012), although not necessarily with an increase in parental anxiety and depression specifically (Loades, Rimes, Ali, Lievesley, et al., 2019). Siblings of affected children and adolescents have elevated anxiety symptoms compared to normative samples, and describe restrictions on family life, uncertainty, social stigma and changes to family roles as some of the consequences (Velleman et al., 2015).

Not only does the illness impact on individuals. CFS also has an impact at societal level. For example, medical consultations and investigations, as well as prescriptions increase considerably around the time of diagnosis and consultation rates are also higher 6 - 10 years before and 6 – 10 years after diagnosis (Collin et al., 2017).

## Treatment

Arguably, the biggest advance since 1995 is that there have been several randomised controlled trials (RCTs) examining the effectiveness of treatments for paediatric CFS. The largest trials have



been in adolescents rather than children and have predominantly focused on Cognitive Behaviour Therapy (CBT) for fatigue. As part of the process of regulating sleep and addressing boom-bust activity patterns, CBT for fatigue targets cognitive processes such as symptom focusing and fear avoidance. CBT aims to improve functioning, facilitate a return to school and social functioning as well as reduce fatigue. There are different modes of delivery including individual, face-to-face (Stulemeijer et al., 2005) and family based (Chalder et al., 2010) approaches. Internet-delivered (Nijhof et al., 2012) and telephone delivered approaches have also been evaluated (Lloyd, Chalder, Sallis, et al., 2012).

These studies found that CBT for fatigue was preferable to waiting list control or other comparator conditions, with recovery rates of approximately 60 to 80%. Long term follow-up found that improvement was maintained over time (Knoop et al., 2008; Lloyd, Chalder, & Rimes, 2012; Nijhof et al., 2013). Notably, most trials have excluded those with severe mental health problems and those who are severely affected, although a small case series found that home-based, family focused CBT showed promise for the latter (Burgess et al., 2018).

Other promising approaches have been developed, most of which incorporate some principles of CBT and draw on other therapeutic approaches. One such approach called the Lightning Process, based on Neurolinguistic Programming (NLP), when offered in addition to treatment as usual (TAU), was more clinically and cost effective compared to TAU alone (Crawley et al., 2017). A pilot trial of physical exercise, which compared 2 variations (aerobic and resistance training), within a multicomponent inpatient programme (including physiotherapy, occupational therapy and psychological therapy), found that both variations led to improvements in quality of life, but only aerobic training decreased fatigue severity (Gordon et al., 2010). Music therapy has been combined with CBT and has been found to be feasible and acceptable, with indications of favourable outcomes in adolescents with postinfectious chronic fatigue (Malik et al., 2020).

Within the UK, some services have introduced more family-based approaches, that combine CBT for fatigue with family therapy techniques, rather than individual CBT and have shown promising outcomes (Chalder, Deary, Husain, & Walwyn, 2010). Some services have also incorporated systemic, narrative therapy and solution-focused approaches have also been incorporated into treatment, which aim to reconnect young people and their families with their skills, values, and hopes and wishes for the future which are often lost within the challenges of living with a chronic health condition. Creative and flexible approaches are used to support those most severely affected (Flannery et al., 2019; Griffin & Christie, 2008). These approaches have had encouraging qualitative feedback from young people and families but are yet to be formally tested.

## What are the issues?

The main advances have been in understanding the epidemiology, describing the clinical features and impact of CFS, and there have been some treatment trials, but there is still much more research needed. Treatments need to be further developed for those who are unable to access specialist, hospital-based services due to geography or because they are so severely affected. Better understanding of the heterogeneity within CFS may enable subtyping, which could inform personalised treatment approaches. We now have a better understanding of what recovery from CFS means for children and adolescents, which will enable more meaningful measurement of outcomes in future trials (Brigden et al., 2018; Harland et al., 2019).

We need to do much more to understand the experience and improve treatment of young people most severely affected, such as those who are bed bound and require inpatient rehabilitation. Case studies of severely affected and qualitative studies to explore their experience could help us to begin

to develop treatment approaches to meet their needs. The larger scale paediatric research studies have often excluded young people with co-morbid mental health difficulties and so questions remain over how to best support this group (Loades & Chalder, 2017). Given that some children and adolescents do not recover, alternative treatment approaches should be developed and evaluated. Despite the vast developments over the past 25 years, children and adolescents living with CFS, and their parents, often report feeling misunderstood and disbelieved by medical and educational services. Service user involvement, dissemination of information and education of professionals in both medical and school settings on the impact of CFS will be essential to continue to improve the experience of and outcomes for children and adolescents experiencing CFS. And at the level of each clinical encounter, it is important to be empathic and to explicitly state that the symptoms are real. Children, adolescents and parents need to know that their concerns are taken seriously and offering practical and emotional support is part of establishing and maintaining engagement in treatment.

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